BIOGRAPHICAL SKETCH

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NAME: Chang, Theresa Li-Yun

eRA COMMONS USER NAME (credential, e.g., agency login): changt03

POSITION TITLE: Associate Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Soochow University, Taipei, Taiwan	B.S.	06/1989	Microbiology
Auburn University, Auburn AL	M.S.	12/1991	Molecular Virology
New York University, New York, NY	Ph.D.	06/1995	Molecular Virology
Yale University, New Haven, CT	Postdoc	1995-1999	Molecular Cell Biology
ADARC/Rockefeller University, New York, NY	Postdoc	1999-2000	HIV-host interaction

A. Personal Statement

I was trained as a virologist and molecular cell biologist, and have been working on the role of innate immunity in HIV transmission and pathogenesis since 2000. Our recent research interests focus on assessing mucosal immune and microbial determinants that modulate HIV infectivity and susceptibility of mucosal T cells in vitro, ex vivo and in explant models. We have demonstrated that sexually transmitted infections (STIs) increase HIV infectivity and susceptibility through innate immune activation. Our recent studies show the interplay between innate immunity and microbiome and the subsequent impact on HIV transmission in women before and after receiving Depo-Provera as well as on gender difference in HIV disease progression in the non-human primate models. We are also interested in identifying host factors important for HIV susceptibility and persistence, and have identified peripheral and mucosal CD4+ T cell subsets that are highly susceptible to HIV infection. Recently, we have demonstrated the immune functions and anti-HIV activity of IFNε, a unique type I IFN and highly abundant in the epithelium of the female reproductive tract (FRT). We are working on the role of IFNε in immune homeostasis, host defense and immune-related reproductive diseases in Ifnε-/- mice and humanized mice.

1. Sperling, R., T. A. Kraus, J. Ding, A. Veretennikova, E. Lorde-Rollins, T. Singh, Y. Lo, A. Quayle, and T. L. Chang. 2013. Differential profiles of immune mediators and in vitro HIV infectivity between endocervical and vaginal secretions from women with Chlamydia trachomatis infection: a pilot study. Journal of Reproductive Immunology 99:80-87. PMCID: PMC3874462
2. Tasker, C., S. Subbian, P Gao, J. Couret, C. Levine, S. Ghanny, P. Soteropoulos, X. Zhao, N. Landau, W. Lu, and T. L. Chang. 2016. Interferon ε protects primary macrophage against HIV infection. JCI Insight. Dec 8; 1(20): e88255. PMCID:PMC 5135270.
3. Couret, J., C. Tasker, J. Kim, T. Sihvonen, S. Fruitwala, A. Quayle, P. Lespinasse, D. Heller, T. L. Chang, 2017. Differential regulation of IFNα, IFNβ and IFNε gene expression in human cervical epithelial cells. *Cell & Bioscience*, 7:57. doi: 10.1186/s13578-017-0185-z. eCollection. PMCID:PMC 5667464.
4. Tasker, C., A. Davidow, N. E. Roche, and T. L. Chang. 2017. Depot medroxyprogesterone acetate administration alters immune markers for HIV preference and increases susceptibility of peripheral CD4+ T cells to HIV infection. Immunohorizons. 1:223-35. doi: 10.4049/immunohorizons.1700047. PMCID:PMC 5703073.

B. Positions and Honors

Positions

2000-2002 Scientist, Osel, Inc. Santa Clara, CA
2001-2002 Visiting Scholar, Stanford University, Palo Alto, CA
2002-2010 Assistant Professor, Department of Medicine, Mount Sinai School of Medicine, New York, NY
2010-2012 Principal Investigator, Public Health Research Institute,
Assistant Professor, Department of Microbiology and Molecular Genetics, UMDNJ-NJMS, NJ
2012-present Associate Professor, Department of Microbiology and Molecular Genetics
Rutgers, the State University of New Jersey (formerly UMDNJ-NJMS)

Other Experience and Professional Memberships

Professional Society Involvement

1991-present American Association for the Advancement of Science, American Society of Virology, Association for Society of Women in Science, Society of Chinese Bioscientists in America
2010-present American Association of Immunologists, New York Academy of Science, American Society of Microbiology
2012-2013 Co-President, Association for Women in Science (AWIS) NYC metro chapter
2014-present Society of Mucosal Immunology.

Grant Review and Editorial Boards

Full Member

2015-2021, The AIDS Immunology and Pathogenesis Study Section, Center for Scientific Review, NIH.

Ad hoc grant reviewer

2006 University of California San Diego, Center for AIDS Research, Developmental grant application.
2011 National Medical Research Council, Singapore.
2012 AIDS Immunology and Pathogenesis Study Section, NIAID, NIH (Ad hoc)
2013 US-China Program for Biomedical Collaborative Research, ZAI1 BDP-A (M2), NIAID, NIH
2013 Mucosal Environment and HIV Prevention (R01), ZAI1 RB-A (J1), NIAID, NIH
2014 Integrated Preclinical/Clinical Program for HIV Microbicides and Biomedical Prevention (IPCP-MBP, U19), ZAI1 BP-A (M2), NIAID, NIH
2014 Targeting Persistent HIV reservoirs (TAPHIR, R21/R33) ZRG1 AARR-K(51), NIAID, NIH
2014 ZAI1 BP-A(J3), Beyond HAART: Innovative Approaches to Cure HIV (U19), NIAID, NIH
2014 Consumer Reviewer, CDMRP Autism Research Program, DOD
2015 ZAI1 KP-A (M1), Mucosal Environment and HIV Prevention II (R01), NIAID, NIH
2016 ZAI1 RB-A (M1), Investigator Initiated Program Project Application (P01), NIAID, NIH
2016 ZAI1 CB-A (J2) Clinical Trial Implementation Cooperative Agreement (U01), NIAID, NIH

Ad hoc Reviewer

Journal of Antimicrobial Chemotherapy, JAIDS, FEBS Letter, Journal of Hepatology, Viral Immunology, Antimicrobial Agents Chemotherapy, Journal of Immunology, PLoS Biology, PloS Pathogens, Future Virology, PLoS One, Journal of Innate Immunity, Journal of Leukocyte Biology, E-book review for Bentham Science Publishers, Antiviral Research, Polymers, Current HIV Research, Virus Research, Journal of Medicine and Medical Science Research, Journal of General Virology, Microbes and Infections, Journal of Molecular Biology, PNAS, Journal of Clinical Investigation, Retrovirology, Antibiotics, Journal of AIDS and Clinical Research, European Respiratory Journal, Experimental and Molecular Pathology, Scandinavian Journal of Immunology, Clinical and Experimental Immunology, mSphere, BMC Women's Health, Science Immunology.

Editorial board member

BioMed Research International, EC Microbiology, Journal Medical Sciences (guest editor), Viruses (guest editor)

Book Editor

HIV-host interactions, ISBN: 978-953-307-442-9, Published in Nov 2, 2011. InTech Open Access Publisher, Croatia.

Awards

1989 First Place, Thesis Contest and Scholarship, Soochow University, Taipei, Taiwan.
1990 Outstanding Achievement in Academic Excellence, Auburn University, Auburn, AL
1991 Heiben Scholarship, New York University, New York, NY
199-1994 University Scholarship/Fellowship in Residence, New York University, New York, NY
1995 Finalist, Helen Hay Whitney Postdoctoral Fellowship
1999 First place poster competition, Tri-State Chinese Biomedical Science Conference, New York, NY
2014 Top 5 reviewers of 2013 awards for JAIDS, basic and translational section.

PATENTS

Chang, C.-H., D. Simpson, T.L.-Y. Chang, X. Qiang, J. A. Lewicki. Lactobacilli expressing biologically active polypeptides and uses thereof. US Patent No. 7,179,458, 2-20-2007. US Patent No. 7,312,076,12-25-2007. US Patent No. 7833791B2, 11-16-2010.

C. Contribution to Science

1. **Human α-defensins in modulation of mucosal HIV transmission**. Mucosal α-defensins are induced in response to infection or inflammation that may impact HIV transmission and pathogenesis. For decades the conventional understanding was that defensins achieved their antimicrobial activities through membrane disruption. We demonstrated that anti-HIV activity of human neutrophil peptide 1 (HNP1) is distinct from CD8 anti-viral factor(s) from long-term nonprogressors (JV, 2003). Importantly, we showed that while HNP1 has a direct effect on the HIV virion under specific conditions, HNP1 inhibits HIV infection mainly by acting on infected cells through modulating signaling pathways. Our data indicated that HNP1 increases epithelial permeability and promotes HIV traversal of the epithelial barrier, which may contribute to increased risks of HIV acquisition in subjects with STIs. Human □-defensins 5 and 6 (HD5 and HD6) are highly abundant in the gut, and are induced in genital epithelial cells in response to STIs. We discovered that HD5 and HD6 contribute to STI-mediated enhancement of HIV infectivity in vitro. These defensins promote HIV infectivity by enhancing HIV attachment. Anti-HIV activity of polyanionic microbicides is diminished in the presence of HD5 and HD6 (JII, 2011), suggesting that mucosal mediators impact the effectiveness of HIV preventative strategies at the mucosa. Our current data indicates that endocervical secretions from women with active chlamydial infection have elevated levels of HD5 and HD6, which are associated with enhanced HIV infectivity of clinical specimens. We also determined the underlying mechanism of defensin regulation in genital epithelial cells through TLR activation and cytokine induction. Taken together, the contributions from my laboratory have demonstrated that defensins are a double-edge sword with respect to HIV transmission, and we have described novel mechanisms by which defensins inhibit or promote HIV infection.

   a. Chang TL, J. Vargas, Jr , A. DelPortillo, M.E. Klotman. 2005. Dual role of alpha- defensin-1 in anti-HIV-1 innate immunity. Journal of Clinical Investigation 115: 765-773. 2005. PMCID: PMC548697
   b. Klotman ME, A. Rapista, N. Teleshova, A. Micsenyi, GA Jarvis, W. Lu, E. Porter, T.L. Chang. 2008. Neisseria gonorrhoeae-induced human defensins 5 and 6 increase HIV infectivity: role in enhanced transmission. Journal of Immunology 180:6176-6185. PMCID: PMC3042429
   c. Rapista, A, J. Ding, B. Benito, NB Neiditch, W. Lu, T.L. Chang. 2011. Human defensins 5 and enhance HIV-1 infectivity through promoting HIV attachment. Retrovirology 8:45-55. PMCID: PMC3146398
   d. Valere K., A. Rapista, E. Eugenin, W. Lu, T. L. Chang. 2015 Human alpha-defensin HNP1 increase HIV traversal of the epithelial barrier: a potential role in STI-mediated enhancement of HIV transmission. Viral Immunology 28:609-615. PMID:2637901.

2. **Modulation of HIV infection by immune activation and sex hormones.** The mucosal surfaces are composed of complex cellular and soluble elements that play an important role in HIV transmission. We have analyzed the role of mucosal immune components and sex hormones in HIV infectivity and susceptibility in vitro, in explant models, and ex vivo under various clinical settings such as STIs or hormonal changes. We have shown that STIs not only promote HIV susceptibility by induction of defensins (see paragraph 1), but promote HIV susceptibility of primary resting CD4+ T cells through TLR2 activation. We demonstrated a novel mechanism of anti-HIV activity of 17β-estradiol in primary macrophages. Our current data indicated that DMPA (Depo-Provera) promoted HIV infection in vitro, in cervical explants, and

ex vivo. DMPA also altered the immunological markers of PBMCs in vitro and ex vivo. Understanding the impact of these biological components on the mucosal environment and HIV infection is crucial for development an effective strategy for HIV prevention.

a. Ding J, Teleshova N, Rapista A, Jarvis GA, Klotman ME, Chang TL. 2010. *Neisseria gonorrhoeae* enhance HIV infection in primary resting CD4+ T cells through TLR 2 activation. *Journal of Immunology* 184:2814-2824. PMCID: PMC3739425
b. Ding J, and T. L. Chang. 2012. TLR2 activation enhances HIV nuclear import and infection through T cell activation independent and dependent pathways. *Journal of Immunology*. 188:992-1001. PMCID: PMC3262879
c. Tasker, C., J. Ding, M. Schmolke, A. Rivera-Medina, A. García-Sastre, and T. L. Chang. 2014. 17β-estradiol protects primary macrophages against HIV infection through induction of interferon-alpha. *Viral Immunology.* 27:140-150. PMCID: PMC4026106
d. Tasker, C., A. Davidow, N. E. Roche, and T. L Chang, 2017. Depot medroxyprogesterone acetate administration alters immune markers for HIV preference and increases susceptibility of peripheral CD4+ T cells to HIV infection. *ImmunoHorizons* (revision).

3. **A new method for HIV prevention.** Together with the team at Osel, Inc., a lactobacillus company, we genetically engineered a primary isolate of lactobacilli, a species of commensal bacteria in the vaginal mucosa, to express two-domain (2D) CD4 proteins. We demonstrated that purified 2D CD4 proteins and engineered lactobacilli expressing 2D CD4 have anti-HIV activities. This strategy has been further developed as a microbicide at Osel and by other investigators.
   a. Chang, T. L.-Y., C.-C. Chang, D. A. Simpson, Q. Xu, P.K. Martin, L. A. Lagenaur, G. K. Schoolnik, D.D. Ho, S. L. Hillier, M. Holodniy, J. A. Lewicki, and P. P. Lee. 2003. Inhibition of HIV infectivity by a natural human isolate of Lactobacillus jensenii engineered to express functional two-domain CD4. PNAS 100:11672-11677. PMCID: PMC208816

4. **Discovery of novel signaling pathways in regulation of cell growth and HIV infection.** At the early stage of my career, I investigated the mechanisms of cell growth and HIV infection in response to immune mediators. I was the first to demonstrate that IL-4, a known inducer for STAT6, activated STAT1, leading to inhibition of colon cancer cell proliferation. This pathway is distinct from IL-4-mediated STAT6 signaling pathways for cell proliferation, and was later demonstrated to play an important role in T cell differentiation. I also discovered that CD8 antiviral factors, found in long-term HIV-infected nonprogressors, inhibit HIV infection through the STAT1 signaling pathway. I demonstrated that RANTES, a ligand for CCR5 receptor, enhances HIV infection by activation of MAP kinase through interaction with glycosaminoglycan.
   a. Chang, T. L.-Y., X.-B. Peng, and X.-Y. Fu. 2000. Interleukin-4 mediates cell growth inhibition through activation of STAT1. J. Biol. Chem. 275:10212-10217. PMID: 10744706
   b. Chang, T. L.-Y., A. Mosoian, R. Pine, M. E. Klotman, and J. P. Moore. 2002. Soluble factor(s) secreted from CD8+ T lymphocytes inhibits human immunodeficiency virus replication through STAT1 activation. J. Virol. 76: 569-581. PMCID: PMC136805
   c. Chang. T. L.-Y., C.J. Gordon, B. Roscic-Mrkic, C. Power, A. E. I. Proudfoot, J. P. M. Moore, A. Trkola. 2002. Interaction of the CC-chemokine RANTES with glycosaminoglycans activates a p44/p42 mitogen-activated protein kinase-dependent signaling pathway and enhances human immunodeficiency virus type 1 infectivity. J. Virol. 76:2245-2254. PMCID: PMC135942

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/theresa.chang.1/bibliography/43907402/public/?sort=date&direction=ascending

D. Research Support

Current Research Support

NIH R01AI110372 Chang, Pei (MPI) 07/01/13 - 06/30/18
Modulation of innate immunity,microbiome and HIV transmission by Depo-Provera
The goal is to determine the profiles of CD4+ T cells and microbiome in women pre and post Depo-Provera treatment and the impact of hormone on HIV infectivity and preference ex vivo and in explant models.

NIH R01AI136948 Chang (PI) 03/01/18-02/28/23
Role of IFNε in immune modulation and HIV infection.
The goal is to determine the immune regulatory role of IFNε in HIV infection and to define the viral determinants involved in IFNε-mediated HIV resistance.

Completed Research Support (Past 5 years)

R01AI110372-02S2 Chang, Pei (MPI), 08/01/15 - 07/31/16
NIH/Gender Supplement
Modulation of innate immunity, microbiome and HIV transmission by Depo-Provera
The goal is to profile transcriptome and microbiome of frozen gut tissues from SHIV-infected RMs.

NIH R01AI081559 Chang (PI) 03/01/10 - 2/28/15, NCE to 2/28/17
Defensins in STI-mediated enhanced HIV infectivity
The goal is to understand the molecular basis of defensin-mediated enhancement of HIV infectivity and the regulation of defensins in vitro and in vivo.

R01AI110372-02S1 Chang (PI) 02/2015 - 03/2017
NIH/ Diversity Supplement
Modulation of innate immunity, microbiome and HIV transmission by Depo-Provera
The goals are to examine the effect of MPA (Depo-Provera) on defensin regulation in endocervical epithelial cells and the subsequent impact on HIV transcytosis and to determine the role of defensins in MPA-mediated enhancement of HIV infection in cervical explant models.

NIH R01AI081559-05S1 Chang (PI), Diversity Supplement 03/01/13 - 02/28/15
Defensins in STI-mediated enhanced HIV infectivity
The goal is to determine the interplay between defensins and broadly neutralizing antibodies on HIV transcytosis and to examine the effect of hormone on defensin regulation.

NIH R21AI093196-01 Chang (PI) 04/01/11 - 03/31/13
HIV-Human Peritoneal Macrophage Interactions
The goal is to dissect the underlying mechanisms of dynamic HIV co-receptor usage in human peritoneal macrophages (PMs), and to establish the contribution of PMs to HIV reservoirs.